New Antiinflammatory Pseudopterosins from the Marine Octocoral *Pseudopterogorgia elisabethae*

Vassilios Roussis, Zhongde Wu,[1] and William Fenical*

Scripps Institution of Oceanography, University of California, San Diego, La Jolla, California 92093-0228

Scott A. Strobel, Gregory D. Van Duyne, and Jon Clardy*

Department of Chemistry-Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

Received March 6, 1990

Eight new diterpene glycosides, pseudopterosins E–L (1–8), along with the methylated aglycon from pseudopterosin E (9), have been isolated from the organic extracts of two individual collections of the tropical Atlantic sea whip *Pseudopterogorgia elisabethae*. The aglycon portions of pseudopterosins E and F (1, 2) are identical with that of pseudopterosin A, but both metabolites have sugar moieties (α-L-fucose for pseudopterosin E and α-D-arabinose for pseudopterosin F) attached at the C-10 hydroxyl. Pseudopterosin G and its monoacetates (pseudopterosins H–J) are C-9 α-L-fucose glycosides. The diterpene aglycon of these molecules is a methyl epimer at the C-7 chiral center, in relation to the aglycons derived from pseudopterosins E and F. Pseudopterosins K and L (7, 8) are α-L-fucosides with the same diterpene skeleton as pseudopterosins E and F, but with the sugar attached at the C-9 hydroxyl. However, the aglycons of pseudopterosins K and L were found to be enantiomeric to those from pseudopterosins E and F (1, 2). The structure of pseudopterosin F was confirmed by X-ray crystallographic analysis, and the other new pseudopterosins were chemically converted to derivatives derived from pseudopterosin F. The new pseudopterosins are superior antiinflammatory agents in comparison to pseudopterosin A. Pseudopterosin E (1) shows very low acute toxicity in mice (LD_{50} > 300 mg/kg) and appears to act by a novel mechanism of pharmacological action.

Sea whips of the genus *Pseudopterogorgia* are among the most chemically prolific of the octocorals in the tropical Atlantic Ocean.[2-8] In an assessment of the biomedical applications of secondary metabolites from this source, we earlier encountered a new class of potent antiinflammatory agents, the pseudopterosins,[6,7] (and seco-pseudopterosins[8]), which are diterpene glycosides from *Pseudopterogorgia elisabethae*. The pseudopterosins A–D[6,7] are chemically novel antiinflammatory and analgesic agents but show acute toxicities in the range of 50 mg/kg in mice. Because of this limitation, we initiated comprehensive studies of *P. elisabethae* from numerous regions in the Caribbean Sea and the tropical Atlantic areas. In this paper, we report the isolation of pseudopterosoins E–J (1–6) and the aglycon 9 from a Bermuda collection of *P. elisabethae*, as well as pseudopterosins K and L (7 and 8) from a Bahamas Islands collection (Great Abaco Island) of the same animal. The new pseudopterosins, and in particular pseudopterosin E, possess superior antiinflammatory properties, and more importantly they are nontoxic in acute assays at levels in excess of 300 mg/kg. In cell studies using human neutrophils, pseudopterosin E inhibits the synthesis of leukotrienes, suggesting that the molecule is an antagonist of lipoxygenases or enzymes higher in the arachidonic acid cascade. Recent studies also indicate that pseudopterosin E inhibits degranulation in the same cells.[9]

P. elisabethae was collected at Bermuda at -35 m depth. Freshly collected animals were stored frozen and subsequently extracted first with chloroform and then with ethyl acetate. From the relatively nonpolar fractions of this extract some of the previously reported pseudopterosins A–D were isolated. Careful examination of the polar fractions of this extract revealed the presence of six more glycosides that exhibited similar TLC acid-charring properties. These compounds were isolated by silica vacuum flash chromatography (isooctane/ethyl acetate gradient) and were further purified by silica HPLC using mixtures of diethyl ether/methanol (95/5). Pseudopterosins E and F (1, 2) were the major components of the polar fractions while the monoacetates, pseudopterosins G–J (3–6), were present in minor quantities. The organisms collected in the Bahamas, at Great Abaco Island, were found to contain exclusively pseudopterosins K and L (7, 8) without any trace of the previously discussed metabolites.

The high-resolution mass spectrum of pseudopterosin E (1) suggested a molecular formula of $C_{26}H_{38}O_6$, thus indicating 8 degrees of unsaturation in the molecule. Since the ^{13}C NMR spectrum contained only eight aromatic and olefinic carbon resonances, the molecule was judged to be tetracyclic. The presence of a fully substituted aromatic ring and a trisubstituted double bond was indicated from a single resonance (δ 5.09 d) in the aromatic and olefinic region in the ^1H NMR spectrum. This was confirmed when the multiplicities of the corresponding carbons were obtained (see Table I). An absorption at 3625–3250 cm^{-1} in the IR spectrum, as well as a pronounced bathochromic shift (from 284 to 295 nm) in the UV spectrum upon addition of base (one drop 5% KOH/MeOH) confirmed the presence of a phenol in the molecule. Four sugar methine carbon resonances in the ^{13}C NMR spectrum (71.7, 69.7, 68.4, 67.3 ppm) and a sugar acetal carbon (103.9 ppm), in conjunction with the presence of five signals in the ^1H NMR spectrum (5.00–3.82 ppm), suggested that the molecule was a diterpene glycoside related to pseudopterosin A. The sugar component was shown to be fucose by proton NMR decoupling experiments, as well as by comparison of ^1H NMR chemical shift data with literature values.[10] Comprehensive analysis of the spectral data

(1) Permanent address: Department of Chemistry, Zhongshan University, Guangzhou (Canton), People's Republic of China.
(2) McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661.
(3) Bandurraga, M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463.
(4) Look, S. A.; Buchholz, K.; Fenical, W. *Experientia* **1984**, *40*, 931.
(5) Look, S. A.; Burch, M. T.; Fenical, W.; Zheng, Q.-t.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.
(6) Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 6238.
(7) (a) Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140. (b) Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1586.
(8) Look, S. A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363.
(9) The antiinflammatory biotesting data were provided by Edward S. Luedke and Robert S. Jacobs at the University of California-Santa Barbara. Complete details of the biological properties of the new pseudopterosins will be published as a separate account.

0022-3263/90/1955-4916$02.50/0

Table I. Selected ^1H and ^{13}C NMR Data for Pseudopterosins E–L (1–8)[a]

	Ps-E (1)[b]		Ps-F (2)[b]		Ps-G (3)		Ps-H (4)		Ps-I (5)		Ps-J (6)		Ps-K (7)		Ps-L (8)	
C no.	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1	3.57 (1 H, m)	35.1	3.58 (1 H, br d, J = 7.7)	35.2	3.67 (1 H, m)	37.1	3.70 (1 H, m)	37.0	3.71 (1 H, m)	37.1	3.69 (1 H, m)	37.1	3.57 (1 H, m)	35.7	3.65 (1 H, m)	35.8
2		39.1		39.2		40.1		40.1		40.1		40.1		39.5		39.6
3		29.6		29.7		28.2		34.3		34.2		34.2		30.2		30.3
4		42.8		42.9		44.1		43.9		44.1		44.0		42.8		43.8
5		27.8		27.9		27.6		27.6		27.6		27.6		27.2		27.3
6		30.3		30.3		31.5		31.2		31.5		31.4		30.2		30.3
7	3.36 (1 H, m)	26.8	3.33 (1 H, m)	26.9	3.36 (1 H, m)	34.2	3.42 (1 H, m)	28.1	3.32 (1 H, m)	28.3	3.34 (1 H, m)	28.2	3.39 (1 H, m)	28.1	3.41 (1 H, m)	28.1
8		126.9		127.1		132.5		132.4		132.5		132.5		133.2		133.2
9		144.6		144.6		142.7		142.3		142.5		142.6		142.2		142.3
10		43.0		142.1		145.4		145.2		145.3		145.5		145.1		145.2
11		126.6		126.7		121.8		121.5		121.9		121.9		121.2		121.4
12		128.0		128.2		135.6		136.0		135.7		135.7		135.1		135.2
13		134.0		134.2		130.6		131.0		130.4		130.5		130.0		130.1
14	5.09 (1 H, d, J = 8.7)	130.2	5.09 (1 H, d, J = 9.0)	130.2	4.91 (1 H, d, J = 9.0)	131.2	4.94 (1 H, d, J = 9.2)	131.2	4.95 (1 H, d, J = 8.9)	131.2	4.93 (1 H, d, J = 9.1)	131.3	5.08 (1 H, d, J = 8.4)	129.6	5.14 (1 H, d, J = 4.0)	129.6
15		128.9		129.0		128.4		128.5		128.4		128.4		128.8		128.6
16	1.67 (3 H, s)	24.8	1.66 (3 H, s)	24.9	1.61 (3 H, s)	25.4	1.66 (3 H, s)	25.4	1.66 (3 H, s)	25.4	1.66 (3 H, s)	25.3	1.63 (3 H, s)	25.6	1.67 (3 H, s)	25.6
17	1.74 (3 H, s)	16.8	1.73 (3 H, s)	16.9	1.67 (3 H, s)	17.5	1.72 (3 H, s)	17.5	1.72 (3 H, s)	17.5	1.71 (3 H, s)	17.5	1.72 (3 H, s)	17.6	1.75 (3 H, s)	17.6
18	1.03 (3 H, d, J = 5.9)	20.3	1.03 (3 H, d, J = 5.7)	20.4	0.96 (3 H, d, J = 4.5)	19.9	1.01 (3 H, d, J = 5.5)	19.9	1.00 (3 H, d, J = 4.9)	19.9	1.00 (3 H, d, J = 5.1)	19.9	1.01 (3 H, d, J = 5.2)	20.9	1.03 (3 H, d, J = 5.9)	20.9
19	1.21 (3 H, d, J = 7.0)	22.1	1.21 (3 H, d, J = 6.9)	22.2	1.11 (3 H, d, J = 6.7)	24.5	1.19 (3 H, d, J = 6.9)	24.4	1.23 (3 H, d, J = 6.8)	24.5	1.15 (3 H, d, J = 7.6)	24.4	1.10 (3 H, d, J = 7.0)	23.8	1.19 (3 H, d, J = 7.2)	23.8
20	2.11 (3 H, s)	11.1	2.12 (3 H, s)	11.5	1.91 (3 H, s)	12.1	2.02 (3 H, s)	11.9	2.01 (3 H, s)	12.0	2.01 (3 H, s)	12.1	1.94 (3 H, s)	10.8	1.99 (3 H, s)	10.8
1′	5.00 (1 H, d, J =3.8)	103.9	5.06 (1 H, d, J = 1.0)	104.1	5.06 (1 H, s)	103.5	5.06 (1 H, d, J = 3.5)	101.9	5.17 (1 H, d, J = 3.6)	103.1	5.09 (1 H, d, J = 3.6)	103.5	5.03 (1 H, br s)	103.4	5.25 (1 H, dd, J = 10.4, 2.8)	102.9
2′	3.82 (1 H, d, J = 2.8)	68.5	4.03 (1 H, m)	68.9	3.89 (1 H, br s)	69.4	5.34 (1 H, d, J = 10.4, 3.5)	71.7	4.29 (1 H, d,, J = 10.4, 3.6)	70.4	4.03 (1 H, dd, J = 10.1, 3.6)	69.5	3.89 (1 H, br s)	69.4	4.30 (1 H, dd, J = 10.4, 4.0)	67.6
3′	3.97 (1 H, dd, J = 8.8, 3.8)	69.7	4.03 (1 H, m)	68.9	4.10 (1 H, br s)	70.6	4.22 (1 H, br d, J = 10.4)	69.1	5.23 (1 H, dd, J = 10.4, 2.5)	74.2	4.32 (1 H, dd, J = 10.1, 2.7)	69.0	4.11 (1 H, m)	70.6	5.75 (1 H, d, J = 9.0)	70.5
4′	4.01 (1 H, m)	71.7	4.03 (1 H, m)	68.7	4.10 (1 H, br s)	72.3	3.96 (1 H, br s)	72.6	4.06 (1 H, br s)	67.4	5.29 (1 H, d, J = 2.7)	73.8	4.11 (1 H, m)	72.4	4.11 (1 H, br s)	74.3
5′	4.48 (1 H, m)	67.3	4.35 (1 H, d, J = 11.9) 3.82 (1 H, dd, J = 12.4, 1.8)	63.8	4.32 (1 H, m)	67.7	4.42 (1 H, q, J = 6.6)	67.8	4.44 (1 H, q, J = 6.8)	67.3	4.44 (1 H, q, J = 7.6)	66.6	4.32 (1 H, m)	67.6	4.45 (1 H, q, J = 6.6)	67.3
6′	1.31 (3 H, d, J = 6.7)	15.5			1.21 (3 H, d, J = 6.3)	16.3	1.38 (3 H, d, J = 6.6)	16.2	1.30 (3 H, d, J = 5.0)	16.2	1.17 (3 H, d, J = 6.6)	16.3	1.22 (3 H, d, J = 6.3)	16.2	1.29 (3 H, d, J = 6.8)	16.5
7′								170.9		171.6		171.9				171.5
8′							2.27 (3 H, s)	20.1	2.08 (3 H, s)	20.9	2.17 (3 H, s)	20.7			2.06 (3 H, s)	20.9

[a] Assignments are based on 2D direct (XHCORR) and long-range proton–carbon correlation experiments performed Ps-E, Ps-F, and Ps-G (1–3). Assignments of 4–8 are based on comparisons with 1–3, as well as 2D proton–proton correlation (COSY) measurements. [b] The NMR solvent used in these cases was a mixture of $CDCl_3$ and CD_3OD. In all the other cases the NMR solvent used was $CDCl_3$.

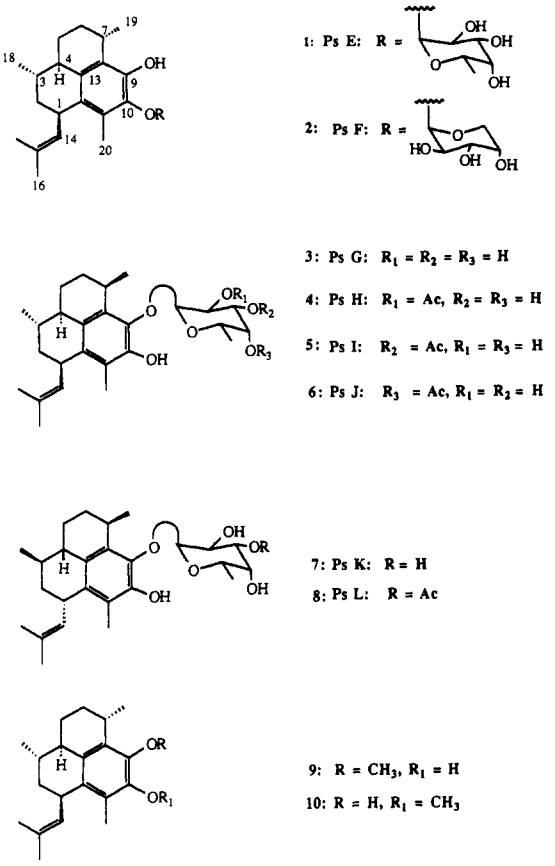

Figure 1. New pseudopterosin derivatives.

suggested that the aglycon portion of pseudopterosin E was identical with that from pseudopterosins A–D. To determine if the only difference was in the sugar component, a comparison of the aglycons from pseudopterosins E and C was desirable. Methylation of pseudopterosin E (**1**) with MeI, followed by acid hydrolysis, yielded the methyl ether **9**. The spectral data of the isolated aglycon **9** were similar to but not identical with those of the methyl ether aglycon **10** derived from pseudopterosin C.[7] The most striking differences between the two aglycons were the chemical shifts of the aromatic carbons in their respective ^{13}C NMR spectra (see Table II). When two-dimensional long-range carbon–proton NMR correlation experiments (COLOC) were performed with pseudopterosin E, they showed a strong correlation of the C-10 carbon with both the aromatic methyl protons (C-20) and the anomeric sugar proton. In the same experiment, no correlations were observed to C-9. The above data suggested that the sugar was attached at the C-10 hydroxyl in pseudopterosin E. Analysis of the proton NMR spectral data further illustrated that compound **1** was an α-fucose pyranoside. Analysis of the coupling constant for the C-1′ anomeric proton illustrated a J value of 3.8 Hz, assignable to an equatorial-axial configuration between the C-1′ and C-2′ protons. While the spectral data were in full accord with the proposed structure for the molecule, an unambiguous proof of the structure was desirable due to its potency as an antiinflammatory agent. Several attempts to obtain a suitable crystal of pseudopterosin E were unsuccessful. An X-ray structure was obtained however for the second major metabolite, pseudopterosin F (**2**), and the X-ray result confirmed our assumption of C-10 glycosidation in these

Table II. Unassigned ^{13}C NMR Data for the Pseudopterosin Methyl Aglycons 9, 10, and 14[a]

9	10	14
145.0 C	144.5 C	144.7 C
142.8 C	143.7 C	143.9 C
134.6 C	134.1 C	135.8 C
132.6 C	130.3 CH	131.5 CH
130.0 CH	130.3 C	130.1 C
129.7 C	129.6 C	128.4 C
129.2 C	126.5 C	126.5 C
120.5 C	126.0 C	125.9 C
61.1 CH_3	60.7 CH_3	60.6 CH_3
41.9 CH	43.5	44.6 CH
39.6 CH_2	39.6	40.2 CH_2
35.7 CH	35.5	37.1 CH
30.7 CH	31.0	34.1 CH
29.8 CH_2	30.0	32.0 CH_2
27.6 CH_3	28.3	28.8 CH
27.5 CH_2	27.5	27.8 CH_2
25.6 CH	25.6	25.4 CH_3
22.8 CH_3	22.9	23.0 CH_3
20.9 CH_3	20.9	20.0 CH_3
17.6 CH_3	17.6	17.5 CH_3
10.6 CH_3	11.2	12.4 CH_3

[a] All spectra were recorded in $CDCl_3$ solutions at 50 MHz. Attached proton analyses were performed by DEPT sequence methods.

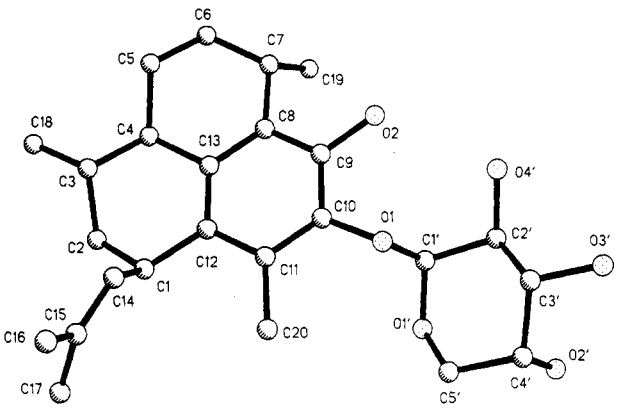

Figure 2. The computer-generated perspective drawing of pseudopterosin F (**2**). The absolute stereochemistry (as shown) was not determined in the X-ray experiment.

metabolites. The methylated aglycons derived from pseudopterosins E and F were compared and found to be identical. A concurrent synthesis of pseudopterosin E, which recently appeared,[11] demonstrated that the sugar in pseudopterosin E was L-fucose.

The structure of pseudopterosin F (**2**) was defined by an X-ray experiment which yielded its relative stereochemistry only. A computer-generated perspective drawing of the final X-ray model of **2**, less hydrogens, is shown in Figure 2. There are two crystallography independent molecules of pseudopterosin F in the asymmetric unit, and, as they have the same molecular conformation, only one is shown. The two independent molecules are roughly related by a transition of 0.50, 0.22, −0.22. The absolute configuration of the molecule was not determined in the X-ray experiment but was later confirmed by comparison of the methyl aglycon derivatives from pseudopterosins F and A. Hydrolysis of pseudopterosin F yielded an arabinose solution with a strong negative rotation, thus indicating the sugar to be of the D configuration.

The third metabolite, pseudopterosin G (**3**), present only in trace quantities in the extract, showed M^+ m/z =

(10) Walker, T. E.; Londoin, R. E.; Whaley, T. W.; Barker, R.; Matwiyoff, N. A. *J. Am. Chem. Soc.* **1976**, *98*, 5807.

(11) Corey, E. J.; Caprino, P. *J. Am. Chem.* Soc. **1989**, *111*, 5472.

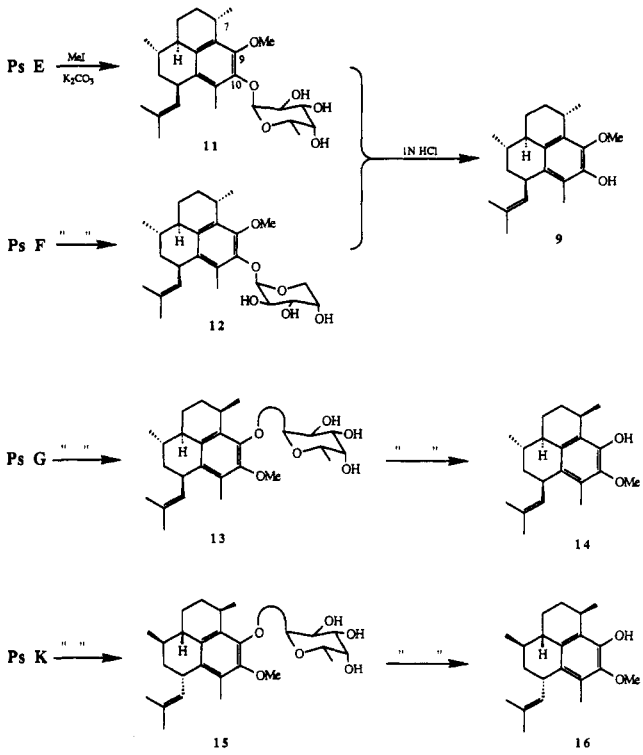

Figure 3. Isolation of aglycon derivatives from pseudopterosins E, F, G, and K.

446.2668, also suggesting a molecular formula of $C_{26}H_{38}O_6$. The position of the sugar in the molecule was illustrated by NOE experiments, performed as before on the methylated aglycon **14** derived from pseudopterosin G. When the methoxy methyl group was irradiated, a significant increase in the intensity of the hydroxyl and aromatic methyl protons was observed, thus illustrating the methyl ether to be positioned at C-10. The same experiment performed on the aglycon **9**, derived from pseudopterosin F, did not show these enhancements. Even though the aromatic carbon resonances in the ^{13}C NMR spectrum of the aglycon **14** (Table II) were very similar to those of the methylated aglycon **10** from pseudopterosin C, there were some subtle ^1H NMR differences that suggested inversion of stereochemistry at one of the chiral centers. Comparison of the ^1H and ^{13}C NMR data of the methylated aglycon **14** with the aglycons from the other pseudopterosins, led to the conclusion that the methyl group at C-7 was inverted. This assumption was confirmed by a series of NOE experiments that showed the spatial proximities of H-1, H-18, H-4, and H-7 on the α-face of the molecule. Irradiation of H-1 enhanced H-18 but not H-3. Additionally, when the H-18 methyl doublet signal was irradiated, a strong increase in the intensity of the H-4 signal was noted. This effect was also observed upon irradiation of the H-7 resonance.

Analysis of the ^1H NMR spectra of pseudopterosins H–J (**4–6**) indicated that these natural products were monoacetate derivatives of pseudopterosins E or G. When treated with $LiAlH_4$, these metabolites were smoothly converted to pseudopterosin G (**3**). Through extensive ^1H NMR decoupling experiments, it was found that pseudopterosins H–J were the C-2′, C-3′, and C-4′ monoacetate derivatives, respectively. The large axial–axial coupling between H-2′ and H-3′ (8.8–10.4 Hz) protons in all the new metabolites showed that the H-2′ protons were axial. The small axial-equatorial coupling (1–3.8 Hz) between H-1′ and H-2′ protons confirmed these compounds were α-glycosides. The L configurations of fucose in pseudopterosins G–J were confirmed by the strong negative rotations observed in the aqueous sugar hydrolysates.

A major, nonpolar constituent of the same extract attracted our attention because it had similar TLC staining behavior as the pseudopterosins. Isolation and purification of this metabolite was performed by silica HPLC (9/1 isooctane/ethyl acetate). From its spectral properties it was clear that the natural product was identical with the methyl aglycon **9** derived by methylation and hydrolysis of pseudopterosin E. It should be noted that pseudopterosins E and F are metabolites unique to the Bermuda collections of *P. elisabethae*. Careful reinvestigation of several of our early Bahamas collections illustrated the presence of pseudopterosins G–J in some, but only in very small amounts.

Pseudopterosins K and L (**7**, **8**) were by far the major constituents of the organic extract of the Bahamas (Great Abaco Island) collections of *P. elisabethae*. The structural relationships of these compounds with those described above were obvious by initial spectral comparisons. The proton NMR spectrum of pseudopterosin K (**7**) showed three singlet methyls (1.94, 1.72, 1.64 ppm) and two doublet methyls (1.22 and 1.01 ppm) along with an olefinic doublet resonance (δ 5.07, d, J = 8.4 Hz), all of which are characterisitc of the pseudopterosin diterpene skeleton. The sugar was assigned as L-fucose by analysis of proton and carbon NMR spectra and ultimately by isolation and optical rotation measurements. Methylation and hydrolysis of pseudopterosin K yielded the aglycon derivative **16**, which was identical but of opposite optical rotation to the same aglycon derivative (**10**) produced from pseudopterosin A. Thus, the aglycon component of pseudopterosin K is enantiomeric to that of pseudopterosins A–F. The monoacetate, pseudopterosin L (**8**), was also isolated and shown to be the 3′-acetate derivative by similar NMR measurements. LAH reduction of pseudopterosin L yielded pseudopterosin K in high yield. Hydrolysis of pseudopterosin K yielded L-fucose, as determined by the strong negative rotation of the aqueous hydrolysate.

Because of the improved pharmacological properties of pseudopterosin E, larger quantities of this less common compound were needed. The large quantities of pseudopterosins A–D available led us to design a synthetic pathway to convert pseudopterosins A–D to pseudopterosin E. Our goal was an interconversion protocol, using protecting groups that could be introduced and removed independently from the aglycon portion of the molecule, which would allow glycosidation at either free hydroxyl position. The *o*-nitrobenzyl ether protecting group, used in peptide synthesis, proved to be the best solution to this problem.[12] *o*-Nitrobenzyl chloride reacts readily with pseudopterosin C under mild basic conditions to provide the ether **17**, in high yield. The advantage of this group is that it is easily removed by photochemical cleavage. This protecting group is also stable under the acidic conditions required to hydrolyze the sugar moiety, thus generating phenol **18**. Treatment of **18** with triethylsilyl chloride yielded the fully protected intermediate **19**. Using these protecting groups, intermediates **18** and **20** were prepared in high yields. It was envisioned that these precursors would allow the glycosidation reaction[13] to be

(12) Amit, B.; Hazum, E.; Fridkin, M.; Patchornik, A. *Int. J. Peptide Protein Res.* **1977**, *9*, 91.

(13) Flowers, H. M.; Levy, A.; Sharon, N. *Carbohydr. Res.* **1967**, *4*, 189. Rachaman, E. W.; Jeanloz, R. W. *Carbohydr. Res.* **1969**, *10*, 429. Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C-13. Rana, S. S.; Barlow, J. J.; Matta, K. L. *Carbohydr. Res.* **1980**, *34*, 353. Takeo, K.; Yasato, T.; Kuge, T. *Carbohydr. Res.* **1981**, *93*, 148. Ogawa, T.; Beppu, K.; Nakabayshi, S. *Carbohydr. Res.* **1981**, C-6.

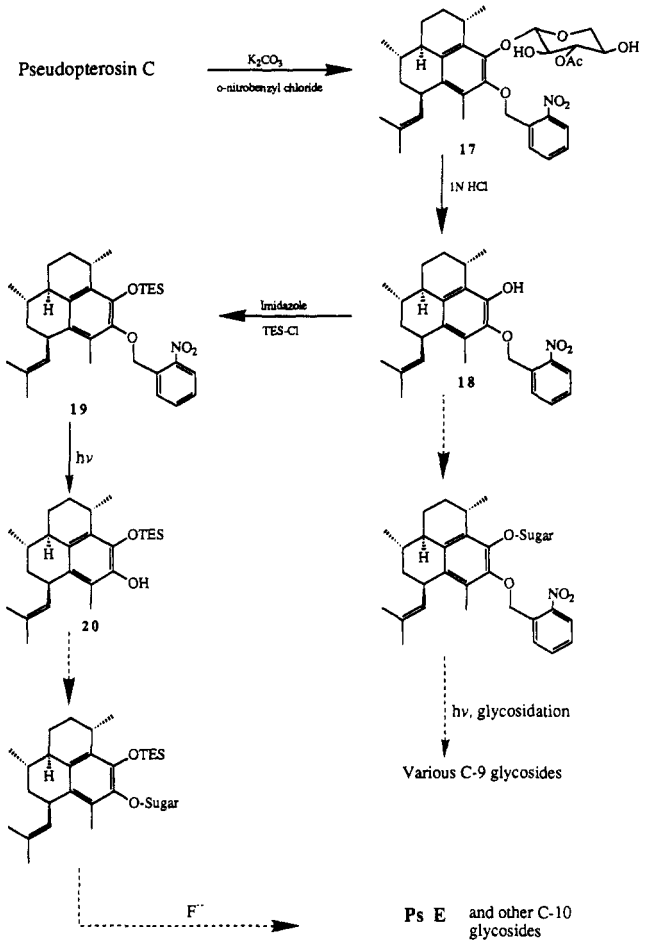

Figure 4. An interconversion scheme for C-9 and C-10 glycosides.

performed at either the C-9 or C-10 hydroxyl positions, thus yielding new glycosides in the pseudopterosin A and E series. Unfortunately, even though numerous glycosidation methods were attempted, the yields of these reactions were always very low.[14,15] Modification of catalysts, solvents, bases, leaving groups,[16] as well as the use of various sugars, failed to improve the reaction yield. Optimizations of the reaction conditions were not pursued since we became aware of the successful synthesis of pseudopterosin E.[11] Nevertheless, our scheme using two versatile protecting groups could provide access to a large variety of new synthetic analogues in the pseudopterosin A and E series.

Experimental Section

General. Proton NMR spectra were recorded in deuteriochloroform or methanol-d_4 at 360 MHz, at the UCSD NMR Center. Carbon NMR spectra were recorded at 50 MHz in the same solvents. High-resolution mass spectra were provided by the Mass Spectrometry Center at UC Riverside, and the High Resolution Mass Spectrometry Center at the University of Iowa.

Pseudopterosin E (1). Purification by HPLC (silica gel, using 5% MeOH in Et_2O) afforded pseudopterosin E as an amorphous white solid: UV (MeOH) λ_{max} 285 (ϵ 3350), 275 (ϵ 2770), 226 (ϵ 20 800); IR (CCl_4) 3500, 3200, 2950, 1450, 1375, 1325 cm^{-1}; $[\alpha]_D$ = −255.0° (c = 0.4, MeOH); HRMS M^+ obsd 446.2681, $C_{26}H_{38}O_6$, calcd 446.2669.

Pseudopterosin F (2). Pseudopterosin F was isolated from the most polar fractions of the organic extract as colorless needles: mp 200 °C dec; UV (MeOH) λ_{max} 284 (ϵ 2400), 275 (ϵ 21 600), 228 (ϵ 12 800); IR (CCl_4) 3400, 2940, 2840, 1450, 1375, 1325 cm^{-1}; $[\alpha]_D$ = −243.2° (c = 0.5, MeOH); HRMS M^+ obsd 432.2503, $C_{25}H_{36}O_6$, calcd 432.2513.

Pseudopterosins G–L (3–8). These compounds, all viscous oils, were purified by normal phase HPLC using mixtures of ethyl acetate in isooctane (50–75% EtOAc/isooctane).

Pseudopterosin G (3): UV (MeOH) λ_{max} 286 (ϵ 1100), 276 (ϵ 850), 229 (ϵ 5600); $[\alpha]_D$ = −56.8° (c = 2.3, $CHCl_3$); HRMS M^+ obsd 446.2668, $C_{26}H_{38}O_6$, calcd 446.2669.

Pseudopterosin H (4): IR (CCl_4) 3500, 2970, 2920, 1750, 1550, 1440 cm^{-1}; $[\alpha]_D$ = −52.1° (c = 1.3, $CHCl_3$); HRMS M^+ obsd 488.2772, $C_{28}H_{40}O_7$, calcd 488.2775.

Pseudopterosin I (5): IR (CCl_4) 3350, 2930, 2870, 1750, 1430, 1370, 1240 cm^{-1}; $[\alpha]_D$ = −44.0° (c = 1.2, $CHCl_3$); HRMS M_+ obsd 488.2774, $C_{28}H_{40}O_7$, calcd 488.2775; UV (MeOH) λ_{max} 286 (ϵ 1900), 275 (ϵ 1450), 228 (ϵ 10 000).

Pseudopterosin J (6): UV (MeOH) λ_{max} 284 (ϵ 2400), 276 (ϵ 1900), 227 (ϵ 13 000); IR (CCl_4) 3450, 3050, 2970, 1780, 1500, 1430, 2990 cm^{-1}; $[\alpha]_D$ = −52.9° (c = 2.2, $CHCl_3$); HRMS M^+ obsd 488.2774, $C_{28}H_{40}O_7$, calcd 488.2775.

Pseudopterosin K (7): UV (MeOH) λ_{max} 284 (ϵ 2300), 277 (ϵ 200); IR (film) 3400, 2920, 2860, 1430, 1370, 1320 cm^{-1}; $[\alpha]_D$ = −111.0° (c = 2.1, $CHCl_3$); HRMS M^+ obsd 446.2678, $C_{26}H_{38}O_6$, calcd 446.2669.

Pseudopterosin L (8): UV (MeOH) λ_{max} 284 (ϵ 1500), 278 (ϵ 1300); IR (film) 3450, 2920, 2850, 1740, 1440 cm^{-1}; $[\alpha]_D$ = −112° (c = 1.1, $CHCl_3$); HRMS M^+ obsd 488.2769, $C_{28}H_{40}O_7$, calcd 488.2775.

Methylation of Pseudopterosin E To Yield Methyl Ether 11. To a stirred solution of pseudopterosin E (1, 77 mg, 0.17 mmol) in dry acetone (15 mL) were added 3 equiv of methyl iodide and potassium carbonate. The reaction mixture was heated to reflux until consumption of the starting material was complete, as judged by TLC analysis. Evaporation in vacuo of the volatile materials was followed by addition of water to the residue, and the aqueous layer was extracted with $CHCl_3$ (3 × 25 mL). Purification by flash chromatography afforded 69 mg (87%) of the expected methylated product 11: ^1H NMR (200 MHz, $CDCl_3$) δ 5.09 (1 H), 5.06 (1 H, d, J = 3.3 Hz), 4.80 (1 H, d, J = 10.3 Hz), 4.43 (1 H, q, J = 6.6 Hz), 4.12 (1 H, m), 3.94 (1 H, br s), 3.85 (1 H, dd, J = 3.3, 10.2 Hz), 3.74 (3 H, s), 3.58 (1 H, d, J = 9.0 Hz), 3.23 (1 H, m), 3.07 (1 H, br s), 2.62 (1 H, br s), 2.04 (3 H, s), 1.75 (3 H, s), 1.68 (3 H, s), 1.37 (3 H, d, J = 6.6 Hz), 1.18 (3 H, d, J = 7.1 Hz), 1.03 (3 H, d, J = 4.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.3, 147.7, 135.5, 134.6, 133.9, 130.4, 104.2, 71.9, 71.5, 69.7, 67.7, 61.5, 42.6, 39.4, 35.9, 30.2, 30.0, 27.8, 27.6, 25.6, 23.4, 20.9, 17.6, 16.3, 14.2, 11.9.

Methylation of Pseudopterosin F To Yield Methyl Ether 12. Pseudopteosin F (2), 100 mg (0.236 mmol), was methylated in a fashion similar to that described above to afford 87 mg (83%) of pure product 12: ^1H NMR (200 MHz, $CDCl_3$) δ 5.18 (1 H, d, J = 3.2 Hz), 5.08 (1 H, d, J = 7.8 Hz), 4.85 (1 H, d, J = 10.1 Hz), 4.24 (1 H, d, J = 10.5 Hz), 4.11 (1 H, br s), 3.91 (1 H, m), 3.73 (3 H, s), 3.55 (1 H, br s), 3.25 (1 H, m), 2.16 (3 H, s), 2.04 (1 H, m), 1.74 (3 H, s), 1.67 (3 H, s), 1.17 (3 H, d, J = 7.1 Hz),1.03 (3 H, d, J = 4.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.6, 147.4, 135.3, 134.4, 133.7, 130.4, 129.3, 127.7, 103.7, 70.7, 69.7, 68.8, 63.9, 61.4, 42.4, 39.2, 35.7, 30.0, 29.8, 27.7, 27.4, 25.6, 23.4, 20.9, 17.6, 11.9.

Methylation of Pseudopterosin G To Yield Methyl Ether 13. Pseudopterosin G (13), 57 mg (0.127 mmol), was treated in a similar manner as above to afford 65 mg (91%) of pure compound 13: ^1H NMR (200 MHz, $CDCl_3$) δ 5.12 (1 H, d, J = 3.7 Hz), 4.96 (1 H, d, J = 9.8 Hz), 4.42 (1 H, q, J = 6.6 Hz), 4.03 (1 H, dd, J = 3.1, 10.0 Hz), 3.95 (1 H, br s), 3.86 (1 H, dd, J = 3.4, 10.0 Hz), 3.74 (3 H, s), 3.66 (1 H, m), 3.34 (1 H, br s), 2.05 (3 H, s), 1.95 (1 H, m), 1.73 (3 H, s), 1.64 (3 H, s), 1.37 (3 H, d, J = 7.1 Hz), 1.24 (3 H, d, J = 6.3 Hz), 1.01 (3 H, d, J = 5.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.7, 137.1, 135.9, 133.5, 130.7, 128.9, 128.0, 104.9, 71.7, 71.5, 69.6, 68.2, 61.1, 44.6, 40.1, 37.1, 34.1, 31.6, 28.8, 27.4, 25.4, 23.5, 19.9, 17.5, 16.4, 12.3.

Methylation of Pseudopterosin K To Yield Methyl Ether 15. Pseudopterosin K (7), 48 mg, was treated according to the already described protocol to afford in high yield compound 15:

(14) Schmidt, R. R.; Reichrath, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 466. Schmidt, R. R.; Moering, V.; Reichrath, M. *Tetrahedron Lett.* **1980**, *21*, 3565.
(15) Thiem, J.; Meyer, B. *Chem. Ber.* **1980**, *113*, 3075.
(16) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond*; Pergamon Press: New York, 1979.

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.14 (1 H, d, J = 3.6 Hz), 5.04 (1 H, d, J = 9.2 Hz), 4.40 (1 H, q, J = 6.7 Hz), 4.15 (1 H, dd, J = 10.0, 2.9 Hz), 3.88 (1 H, br s), 3.78 (1 H, m), 3.73 (3 H, s), 3.59 (1 H, m), 3.37 (1 H, m), 2.05 (3 H, s), 1.74 (3 H, s), 1.67 (3 H, s), 1.33 (3 H, d, J = 6.6 Hz), 1.20 (3 H, d, J = 7.0 Hz), 1.04 (3 H, d, J = 5.8 Hz).

Aglycon Derivative from Pseudopterosin G (14). The methylated derivative of pseudopterosin G (**13**, 33 mg, 0.071 mmol) was dissolved in 5 mL of MeOH. A solution of 2 N HCl (2 mL) was added, and the resulting mixture was heated to 50 °C for 4 h. Evaporation of the solvent in vacuo was followed by extraction of the aqueous layer with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and reduced in vacuo. Purification by HPLC (50% ethyl acetate–isooctane) afforded 18.5 mg (82%) of the desired aglycon **14**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.95 (1 H, d, J = 9.3 Hz), 3.73 (3 H, s), 3.59 (1 H, m), 3.18 (1 H, m), 2.03 (3 H, s), 1.73 (3 H, s), 1.67 (3 H, s), 1.29 (3 H, d, J = 6.7 Hz), 1.01 (3 H, d, J = 4.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.7 (s), 143.9 (s), 135.8 (s), 131.5 (d), 130.1 (s), 128.4 (s), 126.5 (s), 125.9 (s), 60.6 (q), 44.6 (d), 40.2 (t), 37.0 (d), 34.1 (d), 32.0 (t), 28.8 (d), 27.8 (t), 25.4 (d), 22.9 (q), 20.0 (q), 17.5 (q), 12.4 (q); $[\alpha]_D$ = +10.4° (c = 0.7, $CHCl_3$).

Aglycon Derivative from Pseudopterosin F (9). A 65-mg (0.14-mmol) sample of the methyl ether derivative of pseudopterosin F (**12**) was treated in a similar manner as above to afford 26 mg (58%) of the desired product **9**: HRMS M^+ obsd 314.2246, $C_{21}H_{30}O_2$, calcd 314.2247; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.12 (1 H, d, J = 8.8 Hz), 3.76 (3 H, s), 3.61 (1 H, m), 3.31 (1 H, m), 2.05 (3 H, s), 1.75 (3 H, s), 1.67 (3 H, s), 1.24 (3 H, d, J = 7.2 Hz), 1.03 (3 H, d, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.0 (s), 142.8 (s), 134.6 (s), 132.6 (s), 130.0 (d), 129.7 (s), 129.2 (s), 120.5 (s), 61.1 (q), 41.9 (d), 39.6 (t), 35.7 (d), 30.7 (d), 29.8 (t), 27.6 (d), 27.5 (t), 25.5 (d), 22.8 (q), 20.9 (q), 17.6 (q), 10.6 (q); $[\alpha]_D$ = −124.2° (c = 2.2, $CHCl_3$). The optical rotation measured for natural product **9** was $[\alpha]_D$ = −163° (c = 0.9, $CHCl_3$).

Aglycon Derivative from Pseudopterosin E (9). Pseudopterosin E methyl ether **11** (12 mg) was treated in the fashion described above for pseudopterosin F to yield 4.4 mg (54%) of aglycon **9**, $[\alpha]_D$ = −114° (c = 0.1, $CHCl_3$).

Aglycon Derivative from Pseudopterosin K (16). Methyl ether **15**, 25 mg, was treated according to the above-described protocol to afford the aglycon **16** (proton NMR data for the enantiomer have been reported earlier[7]): ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.4 (s), 143.7 (s), 134.1 (s), 130.3 (d), 129.6 (s), 129.6 (s), 126.5 (s), 126.0 (s), 60.7 (q), 43.5 (d), 39.6 (t), 35.5 (d), 30.9 (d), 30.0 (t), 28.3 (d), 27.5 (t), 25.6 (d), 22.8 (q), 21.0 (q), 17.6 (q), 11.2 (q); $[\alpha]_D$ = −34° (c = 0.1, $CHCl_3$). The rotation for the methyl aglycon **10**, derived from pseudopterosin C,[7] is $[\alpha]_D$ = +27.3° (c = 0.3, $CHCl_3$).

***o*-Nitrobenzyl Ether of Pseudopterosin C (17).** Pseudopterosin C (1.0 g, 2.11 mmol) was dissolved in 50 mL of dry acetone. K_2CO_3 (875 mg, 3 equiv) was added to the mixture in one portion, and the solution was stirred at room temperature under nitrogen for 15 min. Subsequently, a solution of *o*-nitrobenzyl chloride (723 mg, 2 equiv) in acetone (5 mL) was added dropwise to the reaction mixture. The reaction mixture was heated at reflux for 8 h. After evaporation of the solvents in vacuo, 100 mL of H_2O was added and the aqueous layer was extracted with $CHCl_3$ (3 × 100 mL). The combined organic solvents were dried over $MgSO_4$ and then reduced in vacuo to a yellow oil. This residue was chromatographed by flash chromatography (isooctane/ethyl acetate mixtures, on TLC grade silica gel) to afford the expected *o*-nitrobenzyl ether **17** (850 mg, 67%) as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.07 (2 H, br d, J = 8.2 Hz), 7.75 (1 H, m), 7.54 (1 H, m), 5.04 (1 H, br d, J = 9.0 Hz), 5.00 (1 H, d, J = 7.3 Hz), 5.69 (1 H, d, J = 14.4 Hz), 4.49 (1 H, d, J = 14.4 Hz), 3.77 (1 H, m), 2.60 (2 H, m), 3.34 (2 H, m), 3.08 (1 H, m), 1.93 (3 H, s), 1.73 (3 H, s), 1.66 (3 H, s), 1.19 (3 H, d, J = 7.1 Hz), 1.03 (3 H, d, J = 5.5 Hz).

***o*-Nitrobenzyl Ether 18.** Compound **17** (400 mg, 0.71 mmol) was dissolved in MeOH (50 mL) and placed in a 150-mL flask equipped with a magnetic stirrer. HCl, 1 N (10 mL), was added to this solution, and the mixture was then heated at 60 °C for 48 h. At the end of this period all the starting material had been converted to a less polar compound (TLC analysis). The mixture was extracted with Et_2O (3 × 100 mL), and the combined organic extracts were dried over $MgSO_4$. The solvents were evaporated in vacuo, and the residue was chromatographed by flash chromatography (isooctane/ethyl acetate mixtures, on TLC grade silica gel) to afford the expected compound **18** (263 mg, 86%) as light yellow needles: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.16 (1 H, dd, J = 8.1, 1.1 Hz), 7.97 (1 H, br d, J = 7.2 Hz), 7.73 (1 H, dd, J = 8.3, 7.8 Hz), 7.53 (1 H, dd, J = 8.5, 8.2 Hz), 5.71 (br s, 1 H, OH), 5.19 (2 H, s), 5.12 (1 H, br d, J = 9.3 Hz), 3.61 (1 H, m), 3.35 (1 H, m), 2.07 (3 H, s), 1.74 (3 H, s), 1.68 (3 H, s), 1.24 (3 H, d, J = 7.0 Hz, 1.12 (3 H, d, J = 5.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.6 (s), 142.0 (s), 134.8 (s), 133.9 (s), 133.8 (d), 133.4 (s), 130.2 (d), 129.8 (s), 129.7 (s), 129.5 (d), 128.7 (d), 126.9 (s), 126.1 (s), 125.0 (d), 71.3 (t), 43.5 (d), 39.6 (t), 35.5 (d), 30.9 (t), 29.9 (d), 28.2 (t), 27.4 (d), 25.6 (q), 22.8 (q), 20.9 (q), 17.6 (q), 11.4 (q).

Triethylsilyl Ether 19. *o*-Nitrobenzyl ether **18** (250 mg, 0.59 mmol) was dissolved in dry DMF (30 mL), and the solution was placed in a dry 3-neck round-bottom flask equipped with a reflux condenser and a nitrogen bubbler. Imidazole (401 mg, 10 equiv) was subsequently added in one portion to the reaction vessel. After stirring for 5 min, triethylsilyl chloride (444 mg, 10 equiv) was added dropwise via syringe to the mixture. The reaction mixture was first stirred at room temperature for 1 h and then warmed to 60 °C for 5 h. Water (50 mL) was added to the mixture, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic solvents were dried over $MgSO_4$ and reduced in vacuo. The residue was chromatographed by flash chromatography (isooctane/ethyl acetate mixtures, on TLC grade silica gel) to afford the expected silyl ether **19** (304 mg, 96%) as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.18 (2 H, m), 7.73 (1 H, m), 7.47 (1 H, m), 5.34 (1 H, d, J = 16.1 Hz), 5.05 (1 H, d, J = 16.1 Hz), 5.09 (1 H, br d, J = 8.0 Hz), 3.56 (1 H, m), 3.33 (1 H, m), 2.00 (3 H, s), 1.70 (3 H, s), 1.67 (3 H, s), 1.21 (3 H, d, J = 6.3 Hz), 1.12 (3 H, d, J = 5.3 Hz), 0.89 (9 H, t, J = 6.3 Hz), 0.62 (6 H, q, J = 6.3 Hz); ^{13}C NMR (50 MHz $CDCl_3$) δ 145.8 (s), 144.6 (s), 135.5 (s), 134.1 (s), 133.5 (d), 131.5 (s), 130.8 (d), 130.2 (s), 129.6 (s), 128.8 (d), 128.4 (d), 127.6 (s), 126.9 (s), 124.6 (d), 70.0 (t), 42.7 (d), 39.5 (t), 35.8 (d), 30.5 (t), 29.9 (d), 28.0 (t), 27.6 (d), 25.7 (q), 22.9 (q), 21.0 (q), 17.6 (q), 11.3 (q), 6.5 (q), 5.9 (t).

Siloxyphenol 20. The bis-protected catechol **19** (375 mg, 0.69 mmol) was dissolved in CH_2Cl_2 (50 mL) and placed into a quartz photoreactor equipped with a reflux condenser and a nitrogen bubbler. Girrard's reagent T (350 mg, 3 equiv) was diluted with MeOH (100 mL) and then added to the reaction mixture. The resulting solution was irradiated with a medium-pressure Hg emission lamp for 6 h until all the starting material had been consumed. Addition of H_2O (100 mL) to the mixture was followed by extraction of the aqueous layer with $CHCl_3$ (3 × 100 mL). The combined organics were dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. The residue was purified by normal-phase HPLC (95% isooctane/ethyl acetate) to afford 252 mg of the expected silyl ether **20** (91%) and 8 mg of unreacted starting material. For **20**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.07 (1 H, br d, J = 8.0 Hz), 5.04 (1 H, s, OH), 3.55 (1 H, m), 3.29 (1 H, m), 2.00 (3 H, s), 1.73 (3 H, s), 1.65 (3 H, s), 1.22 (3 H, d, J = 6.9 Hz), 1.03 (3 H, d, J = 6.8 Hz), 0.97 (9 H, t, J= 6.8 Hz), 0.77 (6 H, q, J = 7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.4 (s), 139.5 (s), 131.4 (s), 130.7 (d), 129.2 (s), 125.8 (s), 123.6 (s), 119.7 (s), 43.5 (d), 39.7 (t), 35.6 (d), 31.3 (t), 30.1 (d), 28.5 (t), 27.6 (d), 25.6 (q), 23.0 (q), 21.0 (q), 17.6 (q), 12.4 (q), 6.6 (q), 5.6 (t).

Absolute Configurations of Sugars. The absolute configuration of fucose in pseudopterosin E was confirmed as L on the basis of a recently reported synthesis.[11] The configuration of arabinose as the D isomer in pseudopterosin F was assigned on the basis of X-ray in conjunction with the determination of the absolute stereochemistry of the aglycon **9**. The configuration of fucose as the L isomer in pseudopterosins G and K was assigned on the basis of the negative rotations observed from crude sugar solutions obtained by hydrolysis under the following conditions: Starting glycoside was combined with 5 mL of methanol and 5 mL of 1 N HCl. The solution was stirred at 60 °C for 4–5 h until starting material had been completely consumed (TLC analysis). The methanol was removed in vacuo, and the aqueous layer was extracted with dichloromethane to remove any unreacted glycoside. The aqueous layer was then reduced to a total volume of 2 mL. Rotations were measured and compared with the rotations obtained from pure D-arabinose, $[\alpha]_D$ −104° (c = 3.0, H_2O),

and L-fucose, $[\alpha]_D$ -75° (c = 10, H_2O), treated in the identical fashion. Results obtained were as follows: For pseudopterosin F (2), $[\alpha]_D$ -17.5° (c = 1.7, H_2O), for pseudopterosin G (3), $[\alpha]_D$ = -20.5° (c = 0.7, H_2O), for pseudopterosin K (4), $[\alpha]_D$ -11.5° (c = 1.0, H_2O).

Single-Crystal X-ray Diffraction Analysis of Pseudopterosin F (2). Pseudopterosin F crystallized as clear prisms, and a specimen roughly 0.4 mm on an edge was selected for further analysis. Preliminary X-ray photographs showed monoclinic symmetry, and accurate lattice constants of a = 11.816 (3), b = 10.294 (4), and c = 21.255 (4) Å, and β = 107.6 (2)°, were determined from diffractometer measured 2θ values. Systematic extinctions, optical activity, and crystal density indicated space group $P2_1$ with two molecules of composition $C_{25}H_{36}O_6 \cdot 2H_2O$ in the asymmetric unit (Z = 4). All unique diffraction maxima with $2\theta > 114°$ were collected on a computer-controlled four-circle diffractometer using graphite monochromated Cu Kα radiation (1.5418 Å) and 1° ω scans. All 3392 independent reflections collected in this manner were used in subsequent calculations. The structure was solved with some difficulty using direct methods and was refined using blocked full-matrix least-squares with anisotrophic heavy atoms and fixed isotropic hydrogens to a conventional crystallographic discrepency index of 6.8%. Additional crystallographic information is available in the supplementary material.

Acknowledgment. This research is a result of combined research and ship funding from the National Science Foundation, Chemistry and Oceanography Divisions, under Grant CHE86-20217, and the California Sea Grant Program, under Grant NA89AA-D-SG140, project no. R/MP-39, and in part by the California State Resources Agency. Research at Cornell University was supported by the New York State Sea Grant Program. We thank the captain and crew of the research vessel *Columbus Iselin* (University of Miami) for their interest and assistance with this work. We gratefully acknowledge the governments of Bermuda and the Bahamas for permission to perform research in their territorial waters.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles for pseudopterosin F (2) and carbon NMR spectra for pseudopterosins (1-8) (16 pages). Ordering information is given on any current masthead page.

A New Synthesis of Aryl Mono *C*-Glycosyl Derivatives of Dialdehyde Sugars

George A. Kraus* and Jianmin Shi

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received February 22, 1990

A new synthesis of mono *C*-glycosyl derivatives of dialdehyde sugars using a Michael addition/aldol condensation sequence has been developed. It is complementary to previously reported methods for the production of *C*-glycosyl compounds. The synthesis involves the Michael addition reaction of an enol silyl ether with acetylbenzoquinone followed by an aldol condensation and subsequent aromatization of the resulting hydroxy ketone. The aldol condensation proceeds only under select conditions and affords the unstable ketols 7 and 15.

Recently, the preparation of *C*-glycosyl compounds has become a very active area. New synthetic methods have been developed for the appendage of aliphatic and aromatic groups onto carbohydrates and for the de novo synthesis of *C*-glycosyl compounds.[1] The synthetic objectives have been either naturally occurring *C*-glycosyl compounds or more complex natural products for which the *C*-glycosyl compound was employed as a synthetic intermediate. Notable synthetic advances include the elegant extensions of the Ferrier reaction by Danishefsky,[2] Fraser-Reid,[3] and others,[4] the preparation of aryl *C*-glycosyl compounds from activated carbohydrates by Kozikowski,[5] Cai,[6] and Schmidt,[7] and the useful modifications of *C*-glycosyl compounds by Horton.[8] Our own contributions have centered around the stereoselective reductions of carbohydrate hemiketals.[9]

We recently reported a direct synthesis of nanaomycin A which proceeded in excellent overall yield.[10] The focal

(1) (a) Hanessian, S.; Pernet, A. G. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 1111. (b) Nicotra, F.; Ronchetti, F.; Russo, G. *J. Org. Chem.* **1982**, *47*, 4459. (c) Reitz, A. B.; Nortey, S. O.; Marianoff, B. E. *Tetrahedron Lett.* **1985**, *26*, 3915. (d) Nicotra, F.; Perego, R.; Ronchetti, F.; Russo, G.; Toma, L. *Carbohydr. Res.* **1984**, *131*, 180. (e) Nicotra, F.; Panza, L.; Ronchetti, F.; Toma, L. *Tetrahedron Lett.* **1984**, *25*, 5937. (f) Chmielewsky, M.; BeMiller, J. N.; Cerretti, D. P. *Carbohydr. Res.* **1981**, *97*, C-1.

(2) (a) Danishefsky, S. J.; De Ninno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. (b) Wincott, F. E.; Danishefsky, S. J.; Schulte, G. *Tetrahedron Lett.* **1987**, *28*, 4951. (c) Isshikawa, Y.; Isobe, M.; Goto, T. *Tetrahedron* **1987**, *43*, 4749.

(3) Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522.

(4) (a) Herscovici, J.; Delatre, S.; Antonakis, K. *J. Org. Chem.* **1987**, *52*, 5691. (b) Herscovici, J.; Muleka, K.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 5653. (c) Grynkiewicz, G.; BeMiller, J. N. *Carbohydr. Res.* **1982**, *108*, 229. (d) De Las Heras, F. G.; San Felix, A.; Fernandez-Resa, P. *Tetrahedron* **1983**, *39*, 1617. (e) Grierson, D. S.; Bonin, M.; Husson, H. P.; Monneret, C.; Florent, J. C. *Tetrahedron Lett.* **1984**, *25*, 4645. (f) Tulshian, D. B.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 518. (g) Yougai, S.; Miwa, T. *J. Chem. Soc., Chem. Commun.* **1983**, 68. (h) Maruoka, K.; Nonoshita, K.; Itoh, T.; Yamamoto, H. *Chem. Lett.* **1987**, 2215. (i) Casiraghi, G.; Cornia, M.; Rassu, G.; Zetta, L.; Gasparri Fava, G.; Ferrari Belicchi, M. *Tetrahedron Lett.* **1988**, *29*, 3323.

(5) Kozikowski, A. P.; Sorgi, K. L., Wang, B. C.; Xu, Z.-B. *Tetrahedron Lett.* **1983**, *24*, 1563.

(6) Cai, M.-S.; Qiu, D.-X. *Carbohydr. Res.* **1989**, *191*, 125.

(7) Hoffmann, M. G.; Schmidt, R. R. *Justus Liebigs Ann. Chem.* **1985**, *12*, 2403.

(8) Martin, M. G. G.; Horton, D. *Carbohydr. Res.* **1989**, *191*, 223.

(9) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752.

0022-3263/90/1955-4922$02.50/0